EXHIBIT T

Review

Critical review of major sources of human exposure to *N*-nitrosamines

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HIGHLIGHTS

- *N*-nitrosamines are found in tobacco, food, water and personal care products.
- Exposure estimated at 1900 to 25,000 ng/day/person, excluding personal care.
- 6000 ± 2950 cancer cases per 1M persons attributable to *N*-nitrosamines.
- $1,940,000 \pm 950,000$ lifetime cancer cases in U.S. attributable to *N*-nitrosamines.
- Up to 92% of exposure and cancer cases avoidable through lifestyle choices.

GRAPHICAL ABSTRACT

ABSTRACT

More than 24 *N*-nitrosamine compounds contribute to the total *N*-nitrosamine (TNA) burden monitored routinely to assess human exposure to this important group of known and suspected human carcinogens. A literature review ($n = 122$) identified multiple sources of human exposure to TNAs, including waters (40 ± 10.5 ng/L; average $\pm$ standard deviation), food and beverages (6.7 ± 0.8 ng/g), tobacco ($16,100 \pm 3650$ ng/g) and personal care products (1500 ± 750 ng/g). Due to source control interventions, levels of TNAs in beer have dropped by about 96% between 1980 and 1990, whereas *N*-nitrosamine levels in other known sources have shown little to no change. Maximum daily TNA exposure in the U.S. in units of ng/d is estimated at $25,000 \pm 4,950$, driven by consumption of tobacco products ($22,000 \pm 4350$), food (1900 ± 380), alcohol (1000 ± 200), and drinking water (120 ± 24). Behavioral choices of individuals in non-occupational settings were calculated to result in a spectrum of exposure values ranging from a lower bound of 1900 ± 380 ng/d to a higher bound of $25,000 \pm 4950$ ng/d, indicating opportunities for a possible 12-fold reduction in TNA exposure to 8% of the above maximum through deliberate choices in diet and lifestyle.

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1. Introduction

N-Nitrosamines have been identified as important environmental pollutants due to their near-ubiquitous presence in many environmental matrices, albeit at typically low concentrations in the nanogram per kilogram and nanogram per liter range. Characterized by a nitroso group bonded to an amine, this hydrophilic family of compounds consists of at least 300 previously documented congeners (Hecht, 1997). While structural diversity is extensive, research has primarily focused on a small subset of *N*-nitrosamine congeners. *N*-nitrosamines are monitored and investigated for their site-specific carcinogenic impact noted in over 30 test animal species (Hecht, 1997) and their well documented occurrence in chlorinated and chloraminated waters (EPA, 2011), food products (Park et al., 2015), tobacco products (Brunnemann and Hoffmann, 1991), and personal care products (Schothorst and Somers, 2005; Wang et al., 2006). *N*-nitrosamine-induced tumors of the liver, lung, esophagus, nasal mucosa, bladder, tongue, forestomach, and pancreas have been documented (Hecht, 1997), with site-specific tumor development being dependent on both the *N*-nitrosamine congener administered and the test species exposed (Hecht, 1997). Site-specific *N*-nitrosamine induced tumors have been observed in specific target organs irrespective of the route of administration (Hill et al., 1973; Bartsch and Montesano, 1984; Lijinsky, 1992; Wilkens et al., 1996; Larsson et al., 2006), and a linear dose-response relationship of *N*-nitrosodimethylamine (NDMA) in the sub-parts-per-million exposure range has been noted along with absence of a discernible "safe threshold" concentration (Peto et al., 1991).

The chemical interaction of nitrous acid with primary aromatic amines was first observed and published by Peter Griess in 1864 (Griess, 1864), and further researched through the work of Baeyer and Caro, and Otto Witt in the 1870s (Witt, 1878). Now in extensive use, the term "nitrosamine" was first introduced by Otto Witt in his 1878 publication to describe "any substituted ammonia which contains, instead of at least one atom of hydrogen, the univalent nitrosyl group, −NO, in immediate connection with the ammoniacal nitrogen" (Witt, 1878). Growth of malignant primary hepatic tumors in animal test species exposed to NDMA was observed in 1956 (Magee and Barnes, 1956), which sparked the development of a large body of literature on the carcinogenicity and toxicity of the *N*-nitrosamine class of contaminants. Their role as environmental carcinogens was first proposed by William Lijinsky in 1970 (Lijinsky, 1970), which fostered research on *N*-nitrosamine

occurrence in environmental media, such as ambient water, aquatic sediments and municipal sewage sludge (Schreiber and Mitch, 2006b; Venkatesan et al., 2014; Zeng and Mitch, 2015; Gushgari et al., 2017). Studies on *N*-nitrosamines mainly have been concerned with the quantification of *N*-nitrosamines from different sources, assessments of cancer impact using animal models, and the modeling of cancer risks related to specific *N*-nitrosamine/cell interactions. Cancer risk of select *N*-nitrosamines, most notably NDMA, has been shown to exceed that of many known potent carcinogens, including: asbestos, benzo[*a*]pyrene, and polychlorinated biphenyls (OEHHA, 2009). Slope factors for cancers attributed to *N*-nitrosamine ingestion or inhalation are available only for a select few *N*-nitrosamines, thus the carcinogenic impact of the class of *N*-nitrosamines is still poorly defined and potentially underestimated.

The International Agency for Research on Cancer (IARC) has classified 24 different *N*-nitrosamines with respect to their carcinogenetic potential to humans, with two congeners being classified as known human carcinogens and the remainder being split between the categories of probably carcinogenic and possibly carcinogenic (Internation Agency for Research on Cancer, 2015). The U.S. Environmental Protection Agency (USEPA) has also listed five *N*-nitrosamines in their two most recent Contaminant Candidate Lists (CCL3 and CCL4) (U.S. Environmental Protection Agency, 2014). Overall, research on *N*-nitrosamines has spurred the development of a number of water quality regulations for select congeners. The World Health Organization's Guidelines for Drinking-Water Quality 4th edition provides a maximum guideline value for NDMA in drinking water of 100 ng/L (Edition, 2011). The State of California has adopted stringent regulations regarding *N*-nitrosamines in drinking water with 10 ng/L notification levels for *N*-nitrosodiethylamine (NDEA), NDMA and *N*-nitrosodi-*n*-propylamine (NDPA). Furthermore, drinking water guidelines for the State of Massachusetts outline a regulatory limit of 10 ng/L for NDMA (EPA, 2015), and Arizona has set regulatory limits for NDMA (1 ng/L), *N*-nitrosodiphenylamine (NDPhA) (7100 ng/L), and NDPA (5 ng/L) in their National Pollutant Discharge Elimination System Permit Program (Arizona Department of Environmental Quality, 2015).

Whereas a fair amount of studies have documented the occurrence of *N*-nitrosamines in environmental matrices (Kim et al., 2013; Rattray and Cochran, 2014; De Mey et al., 2017; Qiu et al., 2017) and attempted to correlate these exposures to site specific tumor occurrence (Stepanov et al., 2014; Fritschi et al., 2015; Gankhuyag et al., 2017; Kao et al., 2017), thus far still lacking are

quantitative analyses of the relative importance of major total N-nitrosamine (TNA) sources on exposure risk and an identification of opportunities for source and exposure reduction. Therefore, the present analysis of the scientific literature was designed to identify sources of total N-nitrosamine exposure for select N-nitrosamines of major concern listed in Table 1 which may offer an opportunity for reduction through individual lifestyle choices. Specifically, average N-nitrosamine levels within commonly contaminated matrices were evaluated in conjunction with dietary and lifestyle data to estimate average daily exposures for select N-nitrosamine congeners.
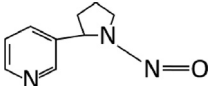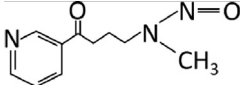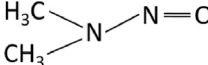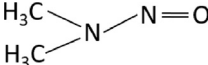
2. Materials and methods

2.1. Literature search
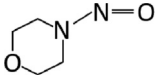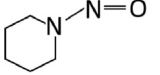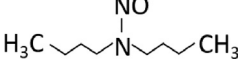
Peer-reviewed literature published prior to 2017 were examined using Google Scholar and Arizona State University's Library One search engines. Search terms used individually and in combinations included chemical names (nitrosamine, N-nitrosamine,

nitrosamines, and N-nitrosamines), media of interest (water, food, personal care product, alcohol, or tobacco), and routes of exposure (ingestion, inhalation, dermal adsorption). We included journal articles focusing on N-nitrosamine concentrations in potable water, food, alcohol, tobacco, and personal care products. Peer-reviewed articles which did not present concentration data within the manuscript or supplemental information were omitted from the analysis, as were articles which were not translated to English from their original publishing language. Journal articles which presented concentrations of N-nitrosamines for products other than the aforementioned five major categories were also omitted from analysis.

Literature for average U.S. smoking statistics, average daily water intake, and average food consumption statistics were identified using the Google Scholar search engine. Average daily smoking values were estimated as 14.2 cigarettes per day per smoker (FSPTCA, 2010) and a U.S. smoking prevalence of 15.1% of the population (Phillips et al., 2017). Information regarding carcinogenic potential and analyte grouping was obtained from the IARC. Oral cancer slope factors were obtained from the U.S. EPA

Table 1
Summary facts on N-nitrosamines covered in this critical review.[a]

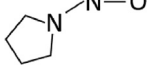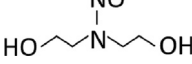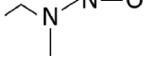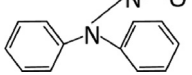| IARC Classification	Congener Name	Congener Structure	U.S. EPA Oral Slope Factor
Group 1 (Carcinogenic to Humans)	N-Nitrosonornicotine (**NNN**)		*Not Available*
	4-(N-Nitrosomethylamino)-1-(3-pyridyl)-1-butanone (**NNK**)		*Not Available*
Group 2A (Probably Carcinogenic to Humans)	N-Nitrosodimethylamine (**NDMA**)		51 $\frac{mg}{kg*d}$
	N-Nitrosodiethylamine (**NDEA**)		150 $\frac{mg}{kg*d}$
Group 2B (Possibly Carcinogenic to Humans)	N-Nitrosomorpholine (**NPIP**)		*Not Available*
	N-Nitrosopiperidine (**NPIP**)		*Not Available*
	N-Nitrosodi-n-butylamine (**NDBA**)		5.4 $\frac{mg}{kg*d}$
	N-Nitrosopyrrolidine (**NPYR**)		2.1 $\frac{mg}{kg*d}$
	N-Nitrosodiethanolamine (**NDELA**)		2.8 $\frac{mg}{kg*d}$
	N-Nitrosomethylethylamine (**NMEA**)		22 $\frac{mg}{kg*d}$
Group 3 (Not Classifiable as to its Carcinogenicity to Humans)	N-Nitrosodiphenylamine (**NDPhA**)		0.0049 $\frac{mg}{kg*d}$

[a] IARC classifications were obtained from the "IARC Monographs on the Evaluation of Carcinogenic Risks to Humans". USEPA Oral Slope Factors were obtained from OEHHA's "Technical Support Document for Cancer Potency Factors 2009 — Appendix A". N-Nitrosamine congener structures were recreated by the primary author from WHO's "Concise International Chemical Assessment Documents" when available, and from "PubChem."

Integrated Risk Integration System (IRIS) (USEPA, 2017) or the California Office of Environmental Health Hazard Assessment (OEHHA) for: NDMA, *N*-nitrosomorpholine (NMOR), *N*-nitrosomethylethylamine (NMEA), *N*-nitrosopyrrolidine (NPYR), NDEA, NDPA, and NDPhA. Inhalation cancer slope factors were also obtained from the U.S. EPA IRIS (USEPA, 2017) database for: *N*-nitrosonornicotine (NNN), 4-(*N*-nitrosomethylamine)-1-(3-pyridyl)-1-butanone (NNK), and NDMA.

2.2. Data extraction and analysis

Publication literature reporting *N*-nitrosamine concentrations by media meeting the eligibility criteria were extracted from Google Scholar and compiled into EndNote citation manager (vX7.7, Thomas Reuters, New York, USA). The final literature set ($n = 122$) was reviewed for establishing average *N*-nitrosamine concentrations in products within the five matrix categories, as well as average U.S. health and product usage statistics. Within the food matrix classification subcategories of contaminated foods were categorized according to the 1992 USDA food pyramid classifications. Individual product concentrations were compiled in Microsoft Excel, and analyzed using the JMP Pro 12.1.0 data analysis software and Microsoft Excel. Figures were created using a combination of Microsoft's Office Suite programs and Origin Pro.

3. Results

3.1. N-nitrosamine contamination data

The exclusion criteria utilized in the literature review resulted in a pool of 122 relevant studies on *N*-nitrosamine occurrence, encompassing contamination of food products, water, tobacco, alcohol, and personal care products. Publications on *N*-nitrosamines have increased in number since the 1950s with a further uptick by 120% from 2000 to 2015, a time period during which regulatory activity also increased for these emerging contaminants (Halden, 2015) and human carcinogens (see Fig. 1).

Out of the 122 studies considered, 56 studies provided quantitative information on some 262 *N*-nitrosamine contaminated food products (Fajen et al., 1979; Goff and Fine, 1979; Hedler et al., 1979; McWeeny, 1983; Scanlan, 1983; Weston, 1983; Spiegelhalder and Preussmann, 1984; Gavinelli et al., 1988; Song and Hu, 1988;

Kubacki et al., 1989; Scanlan et al., 1990; Mavelle et al., 1991; Tricker et al., 1991b; Oliveira et al., 1995; Izquierdo-Pulido et al., 1996; Glória et al., 1997; Mitacek et al., 1999; Domańska-Blicharz et al., 2005; Okafor and Nwogbo, 2005; Yurchenko and Mölder, 2006; Jurado-Sánchez et al., 2007; Yurchenko and Mölder, 2007; Jo et al., 2010; Ozel et al., 2010; Campillo et al., 2011; Jawad, 2012; Kocak et al., 2012; Coffacci et al., 2013; Kim and Shin, 2013; Herrmann et al., 2015; Park et al., 2015; Seo et al., 2015), 140 contaminated nicotine-containing products (Hoffmann et al., 1979; Rühl et al., 1979; Adams et al., 1987; Fischer et al., 1990; Tricker et al., 1991a, 1991b; Mostafa et al., 1994; Österdahl et al., 2004; Wu et al., 2005; Brunnemann and Hoffmann, 1991; Ding et al., 2008; Laugesen, 2008; Rickert et al., 2008; Xiong et al., 2010; Stepanov et al., 2012; Kim and Shin, 2013), 74 contaminated personal care products (Fan et al., 1977; Spiegelhalder and Preussmann, 1984; Schothorst and Stephany, 2001; Schothorst and Somers, 2005), 64 contaminated alcoholic beverages, and 36 potable water *N*-nitrosamine concentrations (Charrois et al., 2004; Zhao et al., 2006; Planas et al., 2008; Wang et al., 2011). Tobacco product concentrations, governed primarily by the tobacco-specific *N*-nitrosamines NNN and NNK (Tricker et al., 1991a; Brunnemann and Hoffmann, 1991), were consistently reported to have the highest levels of *N*-nitrosamines (TNA: $16,100 \pm 3651$ ng/g) of all media categories, followed by personal care products (TNA: 1507 ± 752 ng/g), food products (TNA: 6.7 ± 0.8 ng/g), potable waters (TNA: 39.4 ± 10.5 ng/L), and alcoholic beverages (TNA: 2.9 ± 0.4 ng/L). Nicotine-containing products also constituted the largest range of concentrations of any media (range: 0—326,000 ng/g), followed by personal care products (range: 0—49,000 ng/g), food products (range: 0—120.8 ng/g), potable waters (range: 2.8—309 ng/L), and alcoholic beverages (range: 0—17.4 ng/L). It is important to note that significant variation exists in the concentration of *N*-nitrosamines populating the sub-classes within the matrix categories.

While over 300 congeners of the *N*-nitrosamine class of contaminants have been identified, existing peer-reviewed literature focuses primarily on a select group of *N*-nitrosamines (see Table 1). Studies concerned with the occurrence of *N*-nitrosamines within tobacco products mainly focused on four tobacco-specific *N*-nitrosamines: NNK, NNN, *N*-Nitrosoanatabine (NAT), and *N*-nitrosoanabasine (NAB) (Stepanov et al., 2006, 2012; Xiong et al., 2010;
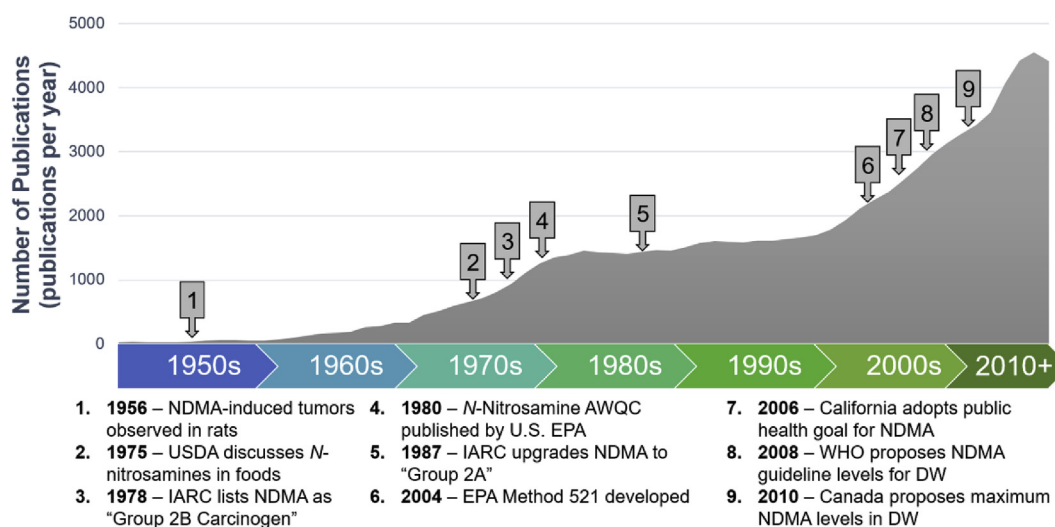
Fig. 1. Publication activity (three-year moving average) and timeline of notable events of *N*-nitrosamine-directed research. Abbreviations: AWQC, Ambient water quality criteria; WHO, World Health Organization; DW, drinking water.

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Kim and Shin, 2013). Two of these *N*-nitrosamines, NNN and NNK, are the only congeners of the *N*-nitroso class that have been identified as 'known human carcinogens' (Internation Agency for Research on Cancer, 2015). Of these tobacco-specific *N*-nitrosamines, tobacco product nitrosamine concentrations were predominantly governed by NNN ($n = 140$, mean: 7400 ± 1500 ng/g), followed by NAT ($n = 102$, mean: 4600 ± 1550 ng/g), NNK ($n = 140$, mean: 3200 ± 1150 ng/g), and NAB ($n = 102$, mean: 950 ± 310 ng/g). Cigarettes were found to have the highest concentrations of the tobacco-specific *N*-nitrosamines (TNA: $52,600 \pm 19,650$ ng/g, range: $590-326,060$ ng/g), followed by cigars (TNA: $45,900 \pm 34,100$ ng/g, range: $11,800-80,000$ ng/g), chewing tobacco (TNA: 5850 ± 2450 ng/g, range: $270-41,400$ ng/g), and snuff products (TNA: 5400 ± 1250 ng/g, range: $19-77,100$ ng/g). Tobacco-specific *N*-nitrosamines were also found in electronic cigarette fluid (TNA: 1430 ± 700, range: $0-3870$ ng/g) and nicotine cessation products (TNA: 450 ± 150 ng/g, range: $0-983$ ng/g) (Hoffmann et al., 1979; Kim and Shin, 2013). Interestingly, concentrations in these products were, respectively, 97.3% and 99.2% lower than the average concentration in traditional cigarettes (Tricker et al., 1991a; Wu et al., 2005; Brunnemann and Hoffmann, 2008). It is important to note that *N*-nitrosamine concentration in dry cigarette tobacco or other nicotine-delivering media do not directly translate to exposure. Instead, nitrosamine concentrations in mainstream and sidestream smoke should be considered for most tobacco related exposure calculations. *N*-Nitrosamine concentrations measured in mainstream (TNA: 1530 ± 670 ng/cigarette, range: $112.7-9700$ ng/cigarette) and sidestream (TNA: 6550 ± 3400 ng/cigarette, range: $340-32,300$ ng/cigarette) significantly violate OEHHA's "no significant risk level" (NSRL) for NNN (500 ng/day) and of NNK (14 ng/day) (OEHHA, 2009).

The high levels of *N*-nitrosamines observed in personal care products is primarily due to the presence of *N*-nitrosodiethanolamine (NDELA), accounting for 99% of all observed *N*-nitrosamines within care products. NDELA contamination in cosmetic products has been attributed to the interaction of di- or triethanolamine, constituents used in many cosmetic formulations, with a nitrosating agent (Fan et al., 1977; Bronaugh et al., 1981; Joo et al., 2015). The remaining 1% of observed contamination stems from NMOR (~0.99%) and NDMA (~0.01%). Cosmetic products (see Fig. 2) were found to have the highest average total *N*-nitrosamine concentration (TNA: $13,000 \pm 8100$ ng/g, range: $400-49,000$ ng/g), but were heavily weighted by two samples with concentrations above

20,000 ng/g. Hair care products (TNA: 1900 ± 1900 ng/g, range: $0-7644$ ng/g), soaps (TNA: 300 ± 150 ng/g, range: $0-3746$ ng/g), shampoos (TNA: 220 ± 50 ng/g, range: $23-1287$ ng/g), and lotions (TNA: 100 ± 25 ng/g, range: $22-230$ ng/g) were all shown to have quantifiable *N*-nitrosamine concentrations with NDELA constituting the major congener in all cases. Two personal care products, an unidentified children's care product (TNA: 1500 ng/g) and a facial cleaner (TNA: 200 ng/g), were averaged together to obtain the "other" category.

N-Nitrosamine concentrations in food and alcohol products (see Fig. 3) represented the largest category of data in this analysis, with data collected from 31 peer-reviewed articles. Currently available literature cites over 300 different reports of *N*-nitrosamine contaminated foods and beverages containing detectable levels of various *N*-nitrosamines, including: fats, oils, and sweets (TNA: $0-44$ ng/g, $n = 21$), meat products (TNA: $0.1-121$ ng/g, $n = 118$), fish products (TNA: $0-43.9$ ng/g, $n = 59$), canned vegetables (TNA: $0.02-40.5$ ng/g, $n = 21$), beverages (TNA: $0.2-45.7$ ng/mL, $n = 13$), condiments (TNA: $0.3-29.59$ ng/g, $n = 10$), grains (TNA: $0.2-4.6$ ng/g, $n = 8$), dairy products (TNA: $0-1.6$ ng/g, $n = 8$), fruit (TNA: 8.1 ng/g, $n = 1$), rice (TNA: 1.5 ng/g, $n = 1$), drink mixes (TNA: 0.9 ng/g, $n = 1$), and tofu (TNA: 0.2 ng/ng, $n = 1$) (Goff and Fine, 1979; Hedler et al., 1979; McWeeny, 1983; Gavinelli et al., 1988; Song and Hu, 1988; Scanlan et al., 1990; Mavelle et al., 1991; Tricker et al., 1991b; Oliveira et al., 1995; Izquierdo-Pulido et al., 1996; Glória et al., 1997; Mitacek et al., 1999; Domańska-Blicharz et al., 2005; Okafor and Nwogbo, 2005; Yurchenko and Mölder, 2006; Jurado-Sánchez et al., 2007; Yurchenko and Mölder, 2007; Jo et al., 2010; Ozel et al., 2010; Campillo et al., 2011; Jawad, 2012; Kocak et al., 2012; Coffacci et al., 2013; Kim and Shin, 2013; Herrmann et al., 2015; Park et al., 2015; Seo et al., 2015). The four food classes with the highest average *N*-nitrosamine concentration levels were identified as fats, oils, and sweets (average TNA: 8.9 ± 3.2 ng/g), meats (average TNA: 8.1 ± 1.4 ng/g), fish (average TNA: 5.6 ± 1.0 ng/g), and vegetables (average TNA: 5.4 ± 1.9 ng/g). NDMA (average: 2.2 ± 0.3 ng/g) was found to have the highest average concentration of all congeners across all food categories, followed by NDBA (average: 1.5 ± 0.5 ng/g), NPYR (average: 1.5 ± 0.2 ng/g), NDEA (average: 0.9 ± 0.3 ng/g), NPIP (average: 0.5 ± 0.1 ng/g), NMOR (average: 0.05 ± 0.01 ng/g), NMEA (average: 0.04 ± 0.01 ng/g), and finally NDPA (average: 0.02 ± 0.01 ng/g).

N-Nitrosamine formation in potable water is a well-documented phenomenon (Charrois et al., 2004; Planas et al., 2008), and thus values for potable water were obtained specifically for a comparison to other matrices and for estimating the attributable risk. The average total *N*-nitrosamine concentration in U.S. potable waters was 39.4 ± 10.5 ng/L, with a range of values between 2.8 and 309.0 ng/L. The average NDMA concentration (17.7 ± 4.7 ng/L) in potable waters exceeded those of all other congeners, but notable levels also were observed for other congeners listed in the following as average concentrations $\pm$ standard deviation: NPIP (7.9 ± 4.0 ng/L), NPYR (5.5 ± 2.6 ng/L), NDEA (4.2 ± 0.8 ng/L), NDBA (1.7 ± 0.6 ng/L), NMOR (0.9 ± 0.2 ng/L), NMEA (0.6 ± 0.1 ng/L), NDPhA (0.6 ± 0.2 ng/L), and NDPA (0.4 ± 0.03 ng/L). While NDMA has been identified as the most prevalent contaminating *N*-nitrosamine in potable waters it accounts for between 5 and 13% of the total *N*-nitrosamine contamination observed in potable waters (Kulshrestha et al., 2010; Dai and Mitch, 2013). Whereas levels of *N*-nitrosamines have been identified in surface water (Schreiber and Mitch, 2006b), wastewater (Krauss and Hollender, 2008; Krauss et al., 2009), biosolids, and freshwater sediments (Venkatesan et al., 2014; Gushgari et al., 2017), these sources are not expected to represent a direct route of human exposure, and thus were omitted from analyses.
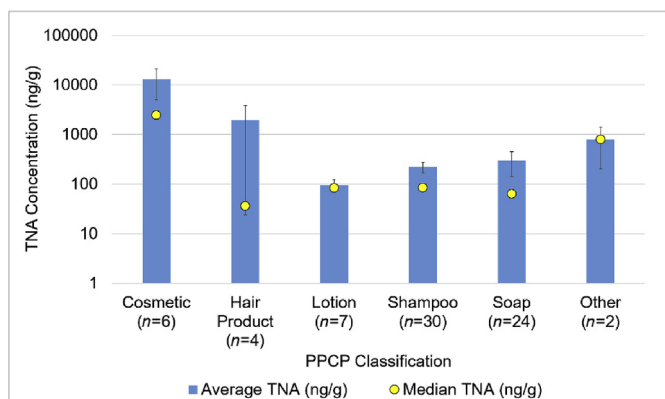
Fig. 2. Average and median TNA concentrations in various categories of personal care products, plotted on a logarithmic scale. Term "*n*" denotes the number of individual product concentrations obtained through literature review. "Other" category denotes products which did not fit into additional categories. Only NDELA was examined in this analysis, due to the lack of data on additional *N*-nitrosamine congeners within PPCPs.
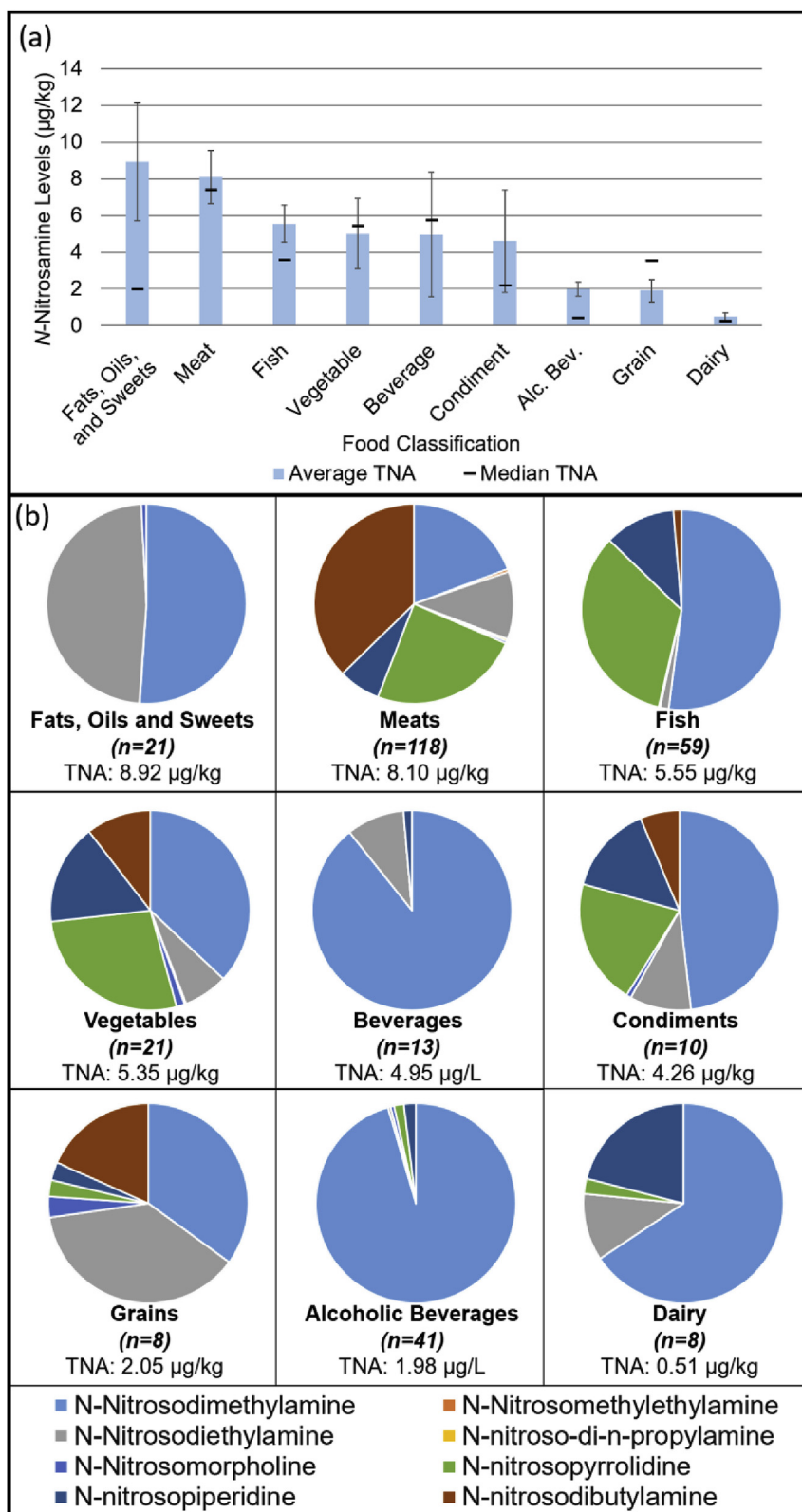
Fig. 3. (*a*) Average and median concentrations (±standard error) of total *N*-nitrosamines (TNA) in various food categories. *(b)* Contribution of individual *N*-nitrosamine congeners to TNA levels detected in various food category, listed in descending order of concentrations reported. Term "*n*" denotes the number of studies one or more *N*-nitrosamines were detected.

In addition to the aforementioned contaminated matrices, there are a number of additional potential sources of human exposure that warrant discussion. Firstly, a number of *N*-nitrosamines have been detected in commonly used rubber and latex products (Fajen et al., 1979; Havery and Fazio, 1982; Altkofer et al., 2005). Car tires, child care products, rubber balloons, and condoms have all shown to not only contain, but readily release *N*-nitrosamines into surrounding matrixes. One source cites that human exposure to *N*-nitrosamines from the use of condoms could exceed exposure from foods 1.5- to 3-fold (Altkofer et al., 2005). Occupational exposure is another important, but selective route of human *N*-nitrosamine exposure. While not applicable to the population as a whole, certain occupations (especially those involved in manufacturing processes) can be associated with a higher risk of *N*-nitrosamine induced tumor development (Spiegelhalder and Preussmann, 1983; Cocco et al., 1996; De Vocht et al., 2007). Furthermore, a considerable number of additional exposure mechanisms have been postulated that theoretically could further increase the total human *N*-nitrosamine exposure, but many of these have not yet been verified and quantified in laboratory or field studies (Havery and Fazio, 1982; Hecht, 1997; Altkofer et al., 2005; Schothorst and Somers, 2005).

3.2. Cancer incidence rate changes in nations consuming large quantities of beer

This literature review also reveals a notable decrease in *N*-nitrosamine concentrations in beers and other malt beverages from the 1980s to the 1990s (see Fig. 4). *N*-Nitrosamine contamination in beer was determined to be a result of malt which had been kilned by direct firing, a formation source that subsequently was reduced by switching to indirect firing of the malt kiln, thereby lowering malt kiln temperatures, and by adding sulfur to the malt (McWeeny, 1983; Lachenmeier and Fügel, 2007).

To gauge the impact of *N*-nitrosamine reduction in beer on cancer incidence, tumor occurrence rates were compared in two countries with high levels of per-capita beer consumption. In the Czech Republic, overall cancer incidence from 1977 to 2011 increased 32% for males and 22.8% for females (Dušek et al., 2010). In this same timeframe, the incidence of tumors of the pancreas, kidney and bladder increased by 56%, 171%, and 82%, respectively (Dušek et al., 2010). In contrast, a cancer registry of the Federal State of Saarland, Germany has noted a decrease in mortality from cancers from 1950 to 2002 for both male and female populations (Becker et al., 2007). However, the overall incidence of cancer (from 1970 to 2002) in this same region did not decrease, and the occurrence of certain site-specific cancers decreased only slightly (laryngeal, −3.3%; lung, −1.8%; stomach, −2.7%). In this same timeframe, lung cancer cases in females increased by 4.9% and prostate cancer cases in males by 5.7%, whereas cancer occurrence rates of all other site-specific cancers showed neither a significant increase nor a decrease (Becker et al., 2007). These findings suggest that while a significant reduction in beer-borne nitrosamines has been achieved, total tumor occurrence and occurrence of site-specific tumors associated with NDMA exposure have nevertheless increased. Observations summarized here in regards to the occurrence of and mortality caused by cancer may be influenced by a variety of factors, including a demographic shift toward an increase in the average age of the general population over the study period and the advent of life-prolonging cancer treatments.

4. Discussion

4.1. N-nitrosamine exposure estimations

Approximate daily *N*-nitrosamine exposure levels were estimated from the data ascertained from the comprehensive literature review and average American consumption habits. Average daily smoking values were estimated as 14.2 cigarettes per day (FSPTCA, 2010), average water intake was estimated to be 3 L per day (Gleick, 1998), and average food intake was estimated from the American Heart Association's 2000-Calorie level dietary guidelines. Daily intake values for food sub-classifications were estimated as 500 g/day of vegetables, 170 g/day of meats, and 168 g/day of fats, sweets and oils (AHA, 2016). This estimation of exposure deliberately omitted uptake from personal care products due to the large uncertainties associated with the use and type of personal care products and the highly variable level of *N*-nitrosamines found therein. Results from the *N*-nitrosamine intake estimates are presented in six categories of varying diets and lifestyle choices as shown in Fig. 5.

Not surprisingly, tobacco use was identified to constitute the largest source of daily *N*-nitrosamine intake across all considered categories, at a rate of $21,800 \pm 4350$ ng/day. Uptake of *N*-nitrosamines from food intake, irrespective of dietary choices, was identified as the second largest source of *N*-nitrosamine exposure, with
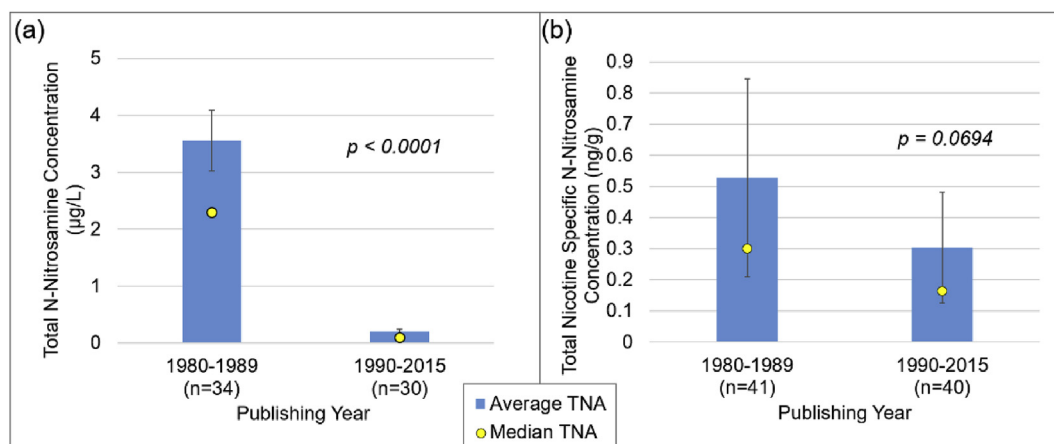
Fig. 4. Representation of *N*-nitrosamine levels in domestic and international beer and tobacco products. (a) Comparison of TNA levels in beer products, from 1980 to 1989 and 1990–2015. Value "*n*" denotes number of reported values obtained from literature. (b) Comparison of TNA levels in mainstream cigarette smoke, from 1980 to 1989 and 1990–2015. Error bars represent ± standard error. Value "*n*" denotes number of reported values obtained from literature.
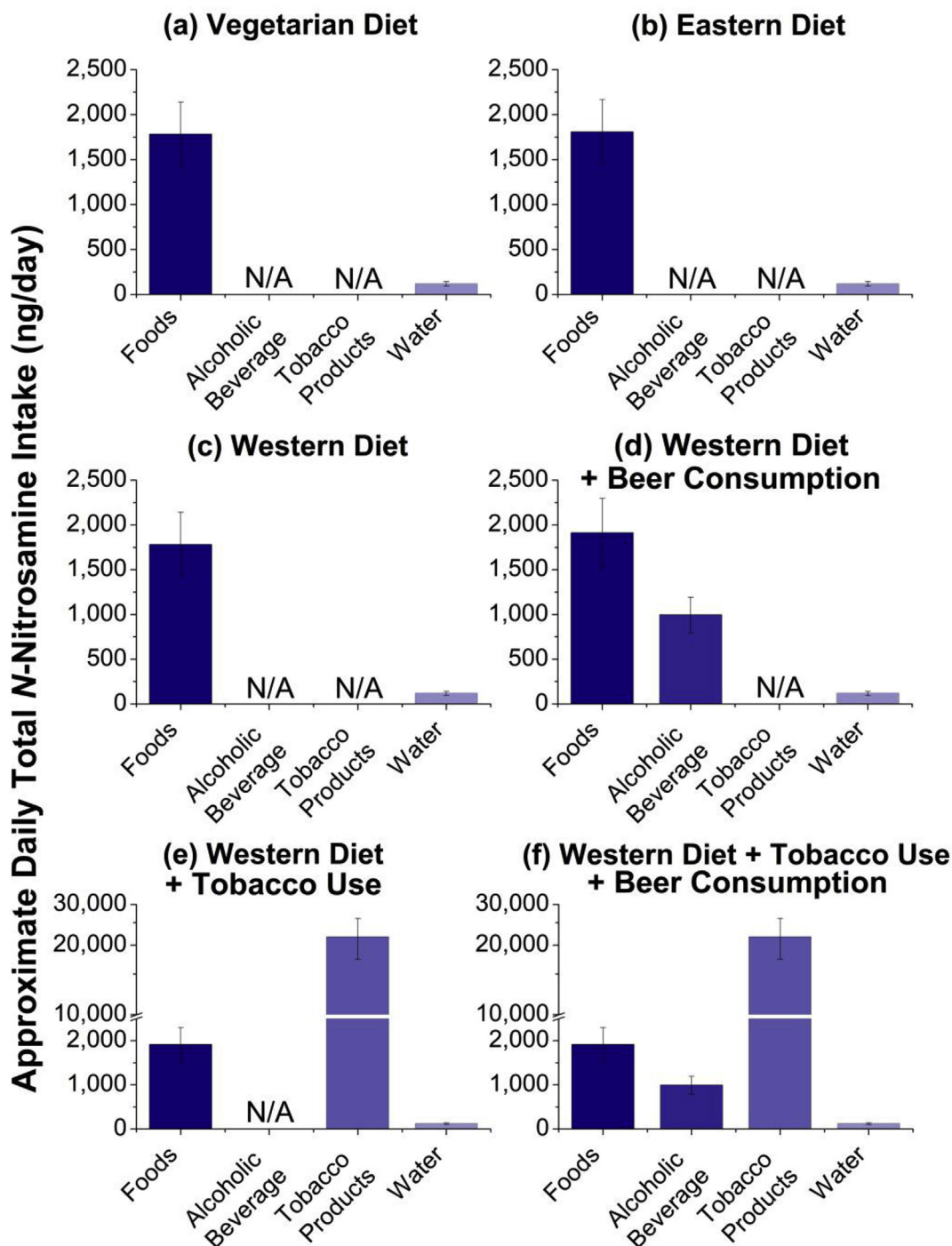
Fig. 5. Estimations of total *N*-Nitrosamine exposure (TNE) by diet and lifestyle. Error bars represent ± 20% of *N*-nitrosamine daily load from the corresponding source.

daily intake values ranging from 1800 ± 350 ng/day (vegetarian diet) to 1900 ± 380 ng/day (western diet). Consumption of beer or other malt beverages was found to contribute an estimated intake of 1000 ± 200 ng/day of *N*-nitrosamine, whereas exposure from ingestion of potable water was consistently found to contribute the smallest daily dose of *N*-nitrosamine exposure at a rate of 120 ± 24 ng/day. Thus, individuals subscribing to a western diet, regularly consuming beer, and smoking tobacco are expected to incur the majority of their daily exposure from tobacco use (88%), with food ingestion (8%), beer consumption (4%), and potable water ingestion (<1%) accounting for the remainder. In contrast,

individuals electing a western diet but refraining from alcohol and tobacco consumption would have a 12-fold lower daily nitrosamine exposure, with the governing factors constituting ingestion of food (94%) and potable water (6%).

4.2. Reduction in the daily N-nitrosamine load

Whereas exposure to *N*-nitrosamines appears to be both pervasive and largely unavoidable, certain lifestyle changes and municipal actions may help to potentially attenuate daily intake. Judging from currently available information, the most important

lifestyle choice an individual can make clearly is to abstain from smoking and use of other tobacco products. Notwithstanding the abundance of adverse health effects and consequences associated with the use of tobacco products, our analysis showed that daily tobacco use contributes a substantial daily concentration (average: $21,800 \pm 4350$ ng/day) of tobacco-specific N-nitrosamines to users. Daily doses of tobacco-related exposure were calculated to exceed by a factor of 10 the baseline exposure from combined intake of water and food, and are also associated with exposure to the only two nitrosamines that are classified by the IARC as 'known human carcinogens' (Internation Agency for Research on Cancer, 2015).

Altering the dietary lifestyle was found to constitute another, less important avenue for reducing the total daily N-nitrosamine exposure of individuals, but unlike cessation of tobacco products, this is a more difficult task that involves altering diets and cooking methods. The literature shows meats and fish products to contain notable concentrations of a wide array of N-nitrosamines whose occurrences have been correlated with the use of preservatives (Herrmann et al., 2015) and heating of food during food preparation (Drabik-Markiewicz et al., 2009) and, lesser so, with additional factors such as pesticide use (Park et al., 2015). Somewhat unexpectedly, the vegetable food category also was found to be associated with a substantial intake of N-nitrosamines (Tricker et al., 1991b; Coffacci et al., 2013; Seo et al., 2015) but this observation may be due to nitrate and nitrite preservatives (Spiegelhalder et al., 1980) added to vegetables rather than to chemistry innate to the plant itself (Coffacci et al., 2013). This modeling of exposure was conducted with the assumption that all vegetable food sources contain the average N-nitrosamine levels calculated from published data. In reality, some vegetables may contain negligible to no levels of N-nitrosamines, whereas others may greatly exceed the average value found through this analysis, leading to a potentially significant variation in exposure levels of individual consumers. While a substantial portion of the population relies on meat and fish products for protein, intake of alternative, plant-based protein sources may aid in N-nitrosamine avoidance. Furthermore, following a teetotaler lifestyle has the potential to reduce daily N-nitrosamine exposure even further.

Proteins are rich in nitrogen and thus deserve consideration as potential vehicles of N-nitrosamine exposure. To further explore this notion, N-nitrosamine exposure from protein sources was examined quantitatively. An average daily protein intake of 51 ± 5 g (Eckel et al., 2013) was assumed, and the resulting exposure from beef, lamb, pork, poultry, and tofu were estimated. Tofu as a protein source was determined to pose the lowest risk, constituting a N-nitrosamine load of 145 ± 10 ng per day per person. This was followed by lamb (1100 ± 50 ng/day), pork (1200 ± 75 ng/day), poultry (1950 ± 230 ng/day), and beef (2350 ± 350 ng/day). This analysis indicates that adhering to alternative sources of protein other than meat (and the cooking habits associated therewith) can reduce the total daily dose of N-nitrosamines an individual incurs. It should also be noted that studies which have examined N-nitrosamine contamination in tofu are rare when compared to studies focusing on other protein sources, and data regarding N-nitrosamine contamination in other vegetarian protein sources was not available, an important limitation of this analysis.

Careful use and avoidance of certain personal care products also has the potential to significantly reduce daily N-nitrosamine exposure, but further research is necessary to understand how impactful this source of exposure actually may be. This literature review did not uncover any notable trends regarding specific personal care products which should be avoided. Many cosmetic and beauty products are applied for vanity purposes and do not constitute a bona fide medical need or necessity, but avoidance of

certain personal care products due to exposure to the N-nitroso class of contaminants may not be universally appropriate. For instance, while high NDMA excretion has been shown due to the consumption of ranitidine (Zeng and Mitch, 2016b), complete avoidance of the medication is likely not feasible for a portion of the population.

There also exist multiple sources of N-nitrosamine intake that are difficult or impossible to avoid, such as exposure from ingestion, absorption and inhalation of N-nitrosamines contained in municipal drinking water (Soltermann et al., 2013). Here, the responsibility for source control and monitoring lies with municipalities, water purveyors and regulatory agencies to protect the general public. While advanced water treatment options have shown to remove N-nitrosamines and their respective precursors (Planas et al., 2008; Plumlee et al., 2008; Farré et al., 2011), the use of residual chlorine or chloramine within distribution lines may negate whatever TNA reduction may have been achieved upstream in the urban water cycle (Zhao et al., 2006).

Furthermore, manipulation of manufacturing methods, addition of stringent "notification" and "action" levels for contamination, and additional regulations all constitute theoretically viable methods of contaminant control, some of which have previously been shown to lead to risk reduction (EPA, 2011). Successful implementation of these methods can be seen through the switch from chlorination to chloramination for the reduction of trihalomethanes and other disinfection byproducts associated with chlorine disinfection (Brodtmann Jr and Russo, 1979; Goslan et al., 2009), and through the reduction of N-nitrosamines in alcoholic beverages and beer products from the 1980s to the 1990s (McWeeny, 1983). It is important to note that the chloramination process has been correlated with higher N-nitrosamine formation rates compared to chlorination (Schreiber and Mitch, 2006a) and therefore is likely not a viable method for N-nitrosamine reduction.

Considering the oral and/or inhalation slope factors indicating high carcinogenic potential associated with these emerging contaminants, municipal regulation of the N-nitroso class of compounds at the Federal level within the United States is still slow to evolve (Halden, 2015). A number of N-nitrosamine congeners have been included in the EPA's contaminant candidate list (CCL), but no maximum contaminant levels or goals have been set for the contaminants within the national primary drinking water regulations. In contrast, a number of U.S. states and other countries have adopted action levels, public health goals, and regulatory limits for some N-nitrosamine congeners, which have been summarized in supplemental information Table S1. While limits for NDMA appear in all N-nitrosamine related regulation, the respective maximum limits of NDMA, as well as regulation of other N-nitrosamine congeners vary. Some reserve exists regarding the true risk of N-nitrosamines from drinking water (Fristachi and Rice, 2007; Chowdhury, 2014a), most notably NDMA, due to the relatively low concentrations observed in this matrix compared to other common sources of exposure (Chowdhury, 2014b). While the basis for this reserve may be valid, the regulation of N-nitrosamines in drinking water, especially for NDMA, likely does benefit the general community. While concentrations in drinking water are generally low compared to other sources of exposure (Zeng and Mitch, 2016a), the high carcinogenic potency of NDMA (Mitch et al., 2003) warrants the frequent monitoring of this carcinogen within potable water sources. Furthermore, areas which may be impacted by industrial activities such as locations of rocket engine testing (Mitch et al., 2003) or rubber manufacturing (De Vocht et al., 2007) may experience notable contamination of groundwater and surface water with N-nitrosamines.

Regulatory oversight in the cosmetics industry could result in a

significant daily *N*-nitrosamine reduction — but regulation of *N*-nitrosamines in personal care products would be difficult due to the numerous existing laws and regulations which currently govern the manufacturing and sale of cosmetics and personal care products. *N*-nitrosamines in these media have the potential for human exposure through two pathways: (1) dermal sorption from applied personal care products and cosmetics through the skin (Bronaugh et al., 1981), and (2) black-water and gray-water contamination which introduces large quantities of *N*-nitrosamines to natural and man-made water systems (Shen and Andrews, 2011; Zeng and Mitch, 2015). Exposure levels due to dermal adsorption (DA) are dependent on many factors, including: type of cosmetic or care product used, volume of product applied, contact time of the product, and the solubility of constituents within product (Bronaugh et al., 1981). Under current U.S. law, no specific tests to demonstrate product safety are required prior to product sales (U.S. Food and Drug Administration, 2016). Furthermore, companies are not required to share their product safety information with the U.S. Food and Drug Administration (FDA) (U.S. Food and Drug Administration, 2016). Addressing these product safety loopholes could lead to the reduction of some of the very high *N*-nitrosamine concentrations found in some cosmetic products (up to 49,000 ng/g) (Fan et al., 1977).

4.3. Comparison of exogenous and endogenous N-nitrosamine formation

While *N*-nitrosamine exposure from various matrices can account for upwards of 25,000 ng/day per person it is important to consider this exposure level alongside endogenous *N*-nitrosamine formation. Significant endogenous *N*-nitrosamine formation has been identified and is considered to be the result of a combination of endogenous nitrosation mainly in the gastrointestinal tract (Hrudey et al., 2013), cell-mediated nitrosation, bacterial nitrosation, and also a result of inhalation of ambient nitrogen oxides (Tricker, 1997). The reactivity and stability of nitrogen and sulfur containing compounds causes favorable biological conditions for endogenous *N*-nitrosamine formation but has been shown to be inhibited by the presence of vitamins C and E, as well as the *S*-nitrosation of thiols (Tricker, 1997). Recent literature suggests that endogenous formation of *N*-nitrosamines governs human exposure to these compounds and may account for 97% of the total *N*-nitrosamine load an individual may experience (Jakszyn and González, 2006). With exogenous exposure only accounting for 3% of the total estimated daily exposure, it is unlikely that avoidance of *N*-nitrosamine contaminated products would result in a significant reduction of *N*-nitrosamine exposure from both exogenous and endogenous sources combined. A reduction of *in vivo* formation may be achieved through avoidance of *N*-nitrosamine precursors, namely nitrite or gaseous oxides of nitrogen (Tricker, 1997), but further research is necessary to assess the potential beneficial impact of this and other reduction strategies.

4.4. Potential biases

While the results presented in this study are relatively well supported by current literature, it is important to consider the potential biases which may have propagated through this study.

Differing treatment of non-detect values within the studies is a potential concern. While many peer-reviewed articles have suggested multiple ways to treat non-detect values (Kayhanian et al., 2002; Krishnamoorthy et al., 2009), most studies which considered *N*-nitrosamine food concentrations treated non-detects as zero. This may not be a true representation of *N*-nitrosamine

concentrations in these foods, and therefore may have indirectly caused an underestimate of the true average *N*-nitrosamine concentrations within food products. Extremely high concentrations of *N*-nitrosamines in food have been reported in the literature. If these values represent "outliers" rather than being representative actual daily doses may be lower than the numbers presented here. The means and medians of the various food classifications were relatively similar, with the only large differences observed for the "fats, oils and sweets" classification, suggesting that exposure averages within this matrix are representative of the actual exposure an individual may be subjected to. Some personal care product sub-categories were impacted by products with high *N*-nitrosamine concentrations, causing a larger difference between median and mean values; thus, discrepancies caused by the use of the median/mean will be more significant for these matrices. A bias in food products routinely analyzed for *N*-nitrosamine also may propagate bias into this analysis, as monitoring efforts are very limited when considering the large number of food products available to consumers. It is possible that many more food items contain one or multiple *N*-nitrosamines, which would further increase the calculated daily doses and may affect the ranking of the various exposure sources considered here.

The *N*-nitrosamine concentrations for potable water used in this analysis are among the highest observed concentrations documented in the literature (Russell et al., 2012) and thus may contribute to an overly conservative estimate of *N*-nitrosamine exposure from drinking water sources. Despite this observation exposure from potable water was identified as a minor exposure pathway, accounting for only between 0.4% and 5% of the total *N*-nitrosamine exposure; if a lower average *N*-nitrosamine concentration of 10 ng/L was used in this analysis, the resulting exposure would account for between 0.1% and 1.6% of the total daily *N*-nitrosamine load. Furthermore, literature suggests that users of municipal water located far downstream from drinking water treatment plant effluent discharge points may be subject to higher *N*-nitrosamine concentrations in their potable water than users closer to the treatment plant (Zhao et al., 2006; Russell et al., 2012) which adds another level of uncertainty to the exposure analysis. Furthermore, few studies have examined *N*-nitrosamine concentrations in additional sources of potable water, such as bottled water or water subjected to point-of-use treatment. These factors suggest that the average exposure due to ingestion of potable water could be more significant for certain individuals based upon unreported factors such as affluence or distance from the servicing drinking water treatment plant. Similar to the literature centering on *N*-nitrosamines in food, most literature dealing with water-related contamination focused on a small percentage of the total *N*-nitrosamine congeners in their analyses, which impedes the ability to fully understand the overall impacts (both environmentally and healthwise) of the *N*-nitroso class. The omission from monitoring efforts of congeners potentially present and important frequently included but was not limited to NNN, NNK, and NDELA. Presence of NDELA has been shown in recycled wastewaters (Dai et al., 2015) but literature pertaining to contamination in other matrices integral to the urban water system are thus far limited. It is also important to note that many commonly encountered carcinogens exist within the natural and built environment — thus *N*-nitrosamine exposure values listed in this paper should be considered alongside the compounding effects of exposure from all potential sources of carcinogen exposure.

4.5. Future scope

One aspect of *N*-nitrosamine exposure which was not examined in this analysis, but could have a large impact on nitrosamine

exposure, is the *in vivo* microbial formation of *N*-nitrosamines within the gut and microbiome. Studies have shown that *in vivo* nitrate reduction to nitrite can increase the formation of mutagenic *N*-nitrosamines within the human body (Lundberg et al., 2004). Intake of high-protein and low-carbohydrate diets have been hypothesized to alter the microbiome community and change intestinal fermentation, subsequently leading to increased levels of hazardous metabolites such as *N*-nitrosamines (Schwabe and Jobin, 2013). This area of research represents a potentially important but poorly understood avenue of human exposure of *N*-nitrosamines.

N-Nitrosamine contamination in personal care products was also identified as an area where a significant increase in research attention is needed. While some product concentrations and experimental dermal sorption values for select *N*-nitrosamines are available, the data is not sufficient enough to perform a meaningful analysis on the carcinogenic impact of using cosmetics and personal care products. It is possible that exposure due to these sources could exceed that of exposure from ingestion of food or water. Research literature has also shown that the *N*-nitroso class is likely much more pervasive than was previously thought, as contamination in unlikely media such as sediments (Gushgari et al., 2017), biosolids (Venkatesan et al., 2014), and fog particles (Wang et al., 2015) has been observed. For this reason, it is important for *N*-nitrosamine monitoring studies to further explore environmental matrices where contamination currently is not suspected or thought to be improbable.

5. Conclusion

N-nitrosamines are a diverse class of chemicals that feature over 300 congeners of known or suspected carcinogenicity. *N*-Nitrosamine contamination is widespread, including tobacco smoke, food, drinking water and personal care products as important exposure sources. Significant uptake of *N*-nitrosamines in humans was identified through the inhalation and ingestion pathways resulting in average total daily doses of $21,800 \pm 4350$ ng/day per person in the U.S. Individual exposure burdens are known to vary significantly as a function of lifestyle choices such as smoking, elected diet and use of personal care products. Avoidance of exposure to *N*-nitrosamine is possible through interventions at the federal, state, municipal, commercial and individual level, with simple interventions such as foregoing smoking and drinking leading to intake reductions of 88% and 4%, respectively. While personal care products have been hypothesized to represent a significant contributor to daily *N*-nitrosamine exposure, currently available data do not allow a calculation of the exposure risk from this source. Future research directions to explore include the monitoring of *N*-nitrosamines specific to personal care products (e.g., to NDELA), and an integration of these and other congeners into risk assessments.

Conflicts of interest

The authors are not aware of any substantive or perceived competing interest concerning this work.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.chemosphere.2018.07.098.

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